16. The antagonist molecule according to Claim 1 wherein said VEGF response is mitogenic activity.

17. (New) The antagonist molecule according to Claim 2, comprising a modification at both position 51 and 60 of the native VEGF.

REMARKS

Claims 1, 2, 4-7, 10-14 and 16 are pending. Claims 3, 8 and 9 have been cancelled without prejudice, disclaimer or admission. A "clean" version of the claims is provided above. Amendments to the claims are indicated in the following section entitled "Version Showing Changes Made".

Claim 1 has been amended to specify a location of modification of the VEGF. Support is found, for example, in Claims 3 and 8 of the application as originally filed.

Claim 2 has been amended to specify that the substitution is not with serine. Support is found, for example, at page 25, lines 8 and 23-24.

Claim 4 has been amended to show proper dependency, in light of the amendment to Claim 1 and cancellation of Claim 3.

Claim 17 has been added as a claim depending from Claim 2, specifying the modification. Support is found, for example, in original Claim 3.

Preliminary Observations

Applicants note that the Office Action Summary lists Claims 1-14 as pending. Applicants point out that a Claim 16 was added in the response mailed May 14, 2001.

Applicants also note that the Office Action summary cites Claims 1-4 and 7-14 as being rejected, however the body of the rejection does not provide a basis for the rejection of Claim 4. Applicants assume that these discrepancies are merely oversights and that they will be rendered moot, in any case, by the present response.

Rejections Under 35 U.S.C. § 112

Claims 1-3 and 7-14 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling specification. Claims 3, 8 and 9 have been cancelled without prejudice, disclaimer or admission. As to the remaining claims, Applicants respectfully traverse.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure . . . coupled with information known in the art without undue experimentation." (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). As MPEP § 2164.01 points out, "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (citing *In re Angstad*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)). Applicants submit that the present disclosure, along with the general knowledge in the field, fully enables the skilled artisan to make and use the claimed invention without undue experimentation.

Applicants also point out that one need not provide every imaginable embodiment of an invention to provide enablement. And, the presence of inoperative embodiments does not necessarily render an invention nonenabled (*see* MPEP § 2164.08(b) and cases cited therein).

The basis of the rejection is that since only one species of substitution is exemplified, *i.e.*, aspartic acid for cysteine, insufficiency guidance is provided to show which other substitutions would be similarly effective to produce the desired result. The Examiner argues that since Pötgens (*J. biol. Chem. 269(52)*:32879-32885 (1994)) did not obtain the same results substituting the VEGF cysteines with serine, the skilled artisan would not know which substitutions to make other than with aspartic acid. Applicants submit that the present application provides ample instruction as to the modifications to be made and the claims leave only routine experimentation to determine the efficacy of a modification other than that exemplified as a working example.

The specification explains that substitutions which are designed to modify the characteristics of a VEGF molecule in a limited manner should be made according to Table I at page 25. The skilled artisan will note that the only conservative substitution recommended in the table for cysteine is serine. The skilled artisan will also note that the working example provided in the specification is not a conservative substitution. Thus, the skilled artisan will understand that Applicants teach a non-conservative substitution of the cysteines. The significance of this is

with the expectation that modifications as claimed will provide the invention. In contrast, Pötgens does not provide such instruction and does not show that antagonists can be obtained by modifying residues 51 and/or 60 of the native VEGF. On the contrary, Pötgens shows that a conservative substitution does not result in a VEGF antagonist and concludes that proper dimerization is necessary to provide such antagonists (p. 32884, right col., paragraph 3). The Examiner states that Pötgens invites investigation of VEGF antagonists. However, this reference provides no instruction as to how to obtain such antagonists. Applicants have provided specific instruction as to how the claimed antagonists are obtained. Therefore, that Applicants have not provided working examples of every single embodiment does not constitute an invitation to investigate. Pötgens provides no suggestion or motivation to make the claimed antagonists while Applicants have shown not only that they may be obtained, but that all species of the claimed invention may be found with routine experimentation.

In view of the discussion above, Applicants submit that Claims 1, 2, 7 and 10-14 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of this rejection is respectfully requested.

Applicants submit that the application is in form for allowance and early notification of such is requested. If there are remaining issues which the Examiner believes may be resolved by telephone, she is invited to call the undersigned attorney at (415) 781-1989.

The Commissioner is hereby authorized to charge any fees, including extension fees, which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-63096/RFT/JJD).

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date January 9, 2002

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VERSION SHOWING CHANGES MADE

1. (Four Times Amended) A vascular endothelial cell growth factor (VEGF) antagonist molecule comprising a variant VEGF polypeptide, said variant polypeptide comprising an amino acid modification of at least one cysteine residue at position 51 and/or 60 of the native VEGF, [wherein said amino acid modification inhibits the ability of said variant polypeptide to properly dimerize with another VEGF polypeptide monomer,] wherein said antagonist molecule is capable of binding to VEGF receptors without significantly inducing a VEGF response, wherein said antagonist molecule is capable of inhibiting a biological activity of a native VEGF protein, wherein said biological activity is induction of a VEGF response.

2. (Amended) The antagonist molecule according to Claim 1, wherein said amino acid modification is a substitution of said at least one cysteine residue with a different amino acid which is incapable of participating in a disulfide bond, wherein said different amino acid residue is not serine.

Claim 3 has been cancelled without prejudice, disclaimer or admission.

4. (Amended) The antagonist molecule according to Claim [3] 2 wherein aspartic acid is substituted for cysteine.

Claims 8 and 9 have been cancelled without prejudice, disclaimer or admission.